AFAMRL-TR-81-33
AD A098 148

EFFECTS OF CNS MANIPULATIONS ON SEIZURES INDUCED BY MONOMETHYLHYDRAZINE ADMINISTRATION IN THE CAT: SPINAL LESIONS

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MARCH 1981

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TECHNICAL REVIEW AND APPROVAL

AFAMRL TR-81-33

The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals, "Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

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FOR THE COMMANDER

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AIR FORCE/56780/16 April 1981 — 150

SECURITY CLASSIFICATION OF THIS PAGE *(When Data Entered)*

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER: AFAMRL-TR-81-33	2. GOVT ACCESSION NO.
3. RECIPIENT'S CATALOG NUMBER	
4. TITLE *(and Subtitle)*: EFFECTS OF CNS MANIPULATIONS ON SEIZURES INDUCED BY MONOMETHYLHYDRAZINE ADMINISTRATION IN THE CAT: SPINAL LESIONS	5. TYPE OF REPORT & PERIOD COVERED: Annual Report Feb. 1, 1980-Jan. 31, 1981
	6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s): M. B. Sterman, Ph.D.; S. S. Bowersox, Ph.D.	8. CONTRACT OR GRANT NUMBER(s): F33615-79-C-0506
9. PERFORMING ORGANIZATION NAME AND ADDRESS: Department of Anatomy and Brain Research Institute, School of Medicine, University of California, Los Angeles, California 90024	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS: 61102F, 2312 - VI - 21
11. CONTROLLING OFFICE NAME AND ADDRESS: Air Force Aerospace Medical Research Laboratory, Aerospace Medical Division, AFSC, Wright-Patterson Air Force Base, Ohio 45433	12. REPORT DATE: March 1981
	13. NUMBER OF PAGES: 18
14. MONITORING AGENCY NAME & ADDRESS *(if different from Controlling Office)*	15. SECURITY CLASS. *(of this report)*: Unclassified
	15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT *(of this Report)*

Approved for public release; distribution unlimited.

17. DISTRIBUTION STATEMENT *(of the abstract entered in Block 20, if different from Report)*

18. SUPPLEMENTARY NOTES

Prepared in cooperation with the Veterans Administration Medical Center, Sepulveda, California 91343

19. KEY WORDS *(Continue on reverse side if necessary and identify by block number)*

sleep spindles
somatosensory deafferentation
monomethylhydrazine

20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)*

This investigation examined the effects of dorsal column lesions on electrocortical activity and susceptibility to monomethylhydrazine induced seizures in cats. Eleven animals, prepared with indwelling cortical electrodes over hindlimb and forelimb projection areas of somatosensory cortex, received bilateral lesions of the dorsal columns at either high (C_1-C_3) or low (C_5-T_1) cervical levels. After a three week postsurgical period, each animal was administered a convulsive dose of monomethylhydrazine. Seizure latency was measured from

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the time of drug injection to the onset of tonic-clonic convulsions. Latency data were compared with those from intact animals (N=18). Comparable pre- and post-lesion EEG recordings were subjected to bandpass filter analysis.

Results indicated a progressive and significant increase in seizure latency with more encephalad dorsal column transection. Further, EEG data showed significant post-lesion enhancement of 12-15 Hz sleep spindle activity over sites corresponding to peripheral receptive fields below the level of the lesions. These findings show that reduced susceptibility to seizures provided by spinal interruption of somatosensory pathways is associated with enhancement of EEG spindle activity over sensorimotor cortex. A similar facilitation of these EEG patterns is seen with chemical and behavioral manipulations known also to provide protection against generalized seizures, suggesting that the release of intrinsic thalamocortical activity may be a common factor in protection against MMH induced seizures.

PREFACE

This research was initiated by the Toxicology Branch, Toxic Hazards Division, Aerospace Medical Research Laboratory, under Project 2312. Experiments were performed from February 1, 1980 to January 31, 1981 under Contract AF F33615-79-C-0506 by the Department of Anatomy and Brain Research Institute, School of Medicine, University of California, Los Angeles, California 90024.

The experiments were conducted by M. B. Sterman, Ph.D of the Veterans Administration Medical Center, Sepulveda, California 91343 and S. S. Bowersox, Ph.D. of the Department of Anatomy, University of California, Los Angeles, California 90024. Kenneth C. Back, Ph.D. was contract monitor for the Aerospace Medical Research Laboratory.

INTRODUCTION

In a previous study, we reported that physical restraint in cats significantly delayed the onset of tonic-clonic convulsions induced by the intraperitoneal injection of monomethylhydrazine (MMH) (Bowersox et al., 1978). It was suggested that this finding related to the enhancement of 12-15 Hz pericruciate cortical EEG patterns, termed sensorimotor rhythms (SMR) (Roth et al., 1967), since these patterns are specifically facilitated by voluntary (Wywicka and Sterman, 1968) or enforced (Holcombe et al., 1979) immobility and, when reinforced by EEG operant conditioning, are known to provide protection against MMH seizures in cats and monkeys (Sterman et al., 1976; Sterman et al., 1978).

Behavioral manipulations which enhance the sensorimotor rhythm in waking animals lead also to a selective facilitation of pericruciate cortical sleep spindle patterns (Sterman et al., 1970). In fact, studies indicate that neural mechanisms responsible for the development of these rhythms over somatosensory thalamocortical projection pathways are essentially identical (Andersen and Andersson, 1968; Harper and Sterman, 1972). Moreover, in addition to their obvious similarities with respect to morphology and cortical distribution (Howe and Sterman, 1972), both patterns appear to be associated with the suppression of peripheral motor excitability (Hongo et al., 1963; Chase and Harper, 1971). Thus, evidence indicates not only that SMR and sleep spindle activity share a common central mechanism, but that they share common functional characteristics as well.

Inasmuch as sleep spindles and waking sensorimotor rhythms originate within ventrobasal thalamus (Andersen and Andersson, 1968; Howe and Sterman, 1972) and appear only in relation to behavioral inhibition (Roth et al., 1967; Wyrwicka and Sterman, 1968; Holcombe et al., 1979), it is likely that reduced somatosensory input contributes to their development. Results of previous investigations support this hypothesis, showing that the spinal interruption of somatosensory afferent projections in acute, lightly anesthetized preparations, induces a continuous, 8-14 Hz rhythmic discharge over ventrobasal thalamocortical projection pathways (Andersson et al., 1971).

With these findings in mind, the present investigation was undertaken to determine whether somatosensory deafferentation influenced MMH seizure susceptibility in chronic, adult cats and, if so, whether these effects were related to the enhancement of 12-15 Hz sensorimotor cortical EEG patterns.

METHODS

Eleven adult cats of either sex, weighing between 2.7 kg and 4.7 kg, were used. Animals were surgically prepared for recording electroencephalographic activity (EEG), eye-movements (EOG), and neck electromyograms (EMG). Surgical procedures were performed under pentobarbital sodium (Nembutal; 35 mg/kg) anesthetic. EEG activity was recorded over sensorimotor and posterolateral cortex using stainless-steel jewelers' screws (0.8 mm diameter) threaded into the calvarium. EEG recordings were referenced to a stainless-steel screw threaded into the skull over the most rostral tip of the frontal sinus. Two additional screws were placed medially and laterally into the orbit within the frontal sinus to record eye movements, and

braided steel wires, insulated to within 5 mm of their tips, were inserted bilaterally into the nuchal musculature for recording muscle activity. Bipolar stainless-steel wires (250μ diameter), insulated to within 1 mm of their tips, were inserted into subcortical sites. All electrodes were soldered to a Winchester connector which was then affixed to the skull with dental acrylic. After a minimum two-week postsurgical recovery period, polygraphic recordings were obtained from each animal. A minimum of three recordings, each containing at least two REM periods, were obtained over consecutive days. Sessions were initiated at approximately the same time each day. Animals were recorded in a large (75 cm X 75 cm X 95 cm), double-walled, LeHigh Valley chamber equipped with positive ventilation and a transparent viewing window which permitted diffuse ambient lighting. During experimental procedures, animals were provided food and water ad libitum and access to a litter box. Electrographic data were collected simultaneously on a Grass Model 78B polygraph and magnetic tape recorder (Sangamo, Model 5914) for further analysis.

After the last prelesion baseline recording session, the dorsal columns were transected at either the high-cervical (C_1-C_3) or low-cervical (C_5-T_1) level. Spinal sites were located by external landmarks and referenced to the atlas of Crouch (1969). Observing strict aseptic technique, the spinal cord was exposed by laminectomy and the dorsal columns were transected by inserting a scalpel blade (Bard-Parker #11) 1-2 mm into the dorsal surface then extending the cut laterally in a 45-degree arc to the level of the dorsal roots. After completing the section, the lesion site was packed with absorbable gelatin and the overlying musculature and skin sutured. The animal was then removed to a holding chamber and allowed to recover before being returned to the home cage.

After an 18-21 day recovery period, three additional postlesion baseline polygraphic recordings were obtained. Recording parameters were identical to those used for prelesion baselines. After the last postlesion recording session, each animal was deprived of food for a minimum of twelve hours then administered an intraperitoneal injection of MMH at the established convulsive dosage of 10 mg/kg. Behavior was monitored continuously; prodromal behaviors were tabulated together with their times of onset, and seizure latency was determined as the time from drug injection to the onset of tonic-clonic convulsions. Pentobarbital sodium was administered during the tonic phase of the seizure to prevent further convulsions, and the animal was allowed to recover. Seizure latency data were compared with previously reported normative standards for intact animals (Sterman, 1976; Sterman et al., 1977; Shouse and Sterman, 1979).

At the end of the experiment, animals were killed by an overdose of pentobarbital sodium and perfused with 9% saline followed by 10% formalin. Alternate 80μ sections of brain and spinal cord were stained for Nissl substance (thionin) and examined for electrode and lesion site verification.

The incidence of 12-15 Hz sleep spindle activity over medial (A:23, L:2-5) and lateral (A:23, L:10-12) sensorimotor cortex was measured in two, five-minute segments of quiet-sleep from each pre/postlesion baseline recording. Samples consisted of the last six minutes of quiet-sleep preceding REMs onset and were chosen from the first and last REM-cycle of each record. This sample length corresponded to the mean duration of quiet-sleep episodes in adult cats (Sterman et al., 1965) and allowed comparable assessments of spindle-burst activity in pre- and postlesion recordings. The last minute of each sample was not evaluated, since this segment contained transitional EEG state patterns (Ursin and Sterman, 1981). Spindles were measured automatically by passing tape recorded EEG signals through

a pair of inversed, twin-T filters (peak signal detection at 13.5 Hz, 6 dB down at 12 Hz and 15 Hz). Filter output was fed into level detector circuits which specified the voltage necessary to activate a relay. Relay voltage was passed through a logic timing circuit which specified the length of time the relay had to remain activated in order to trip a counter. A spindle was scored each time the relay output met minimum duration and interval criteria. Spindle duration (0.5 second) and interspindle interval (1.25 seconds) criteria were the same for all animals; however, due to individual differences in spindle morphology, the spindle amplitude criterion was determined empirically for each animal to correspond with visually detected spindle patterns. Once established, this amplitude criterion remained constant across all recording trials. A sample tracing showing bandpass analysis of 12-15 Hz spindle activity in a segment of quiet-sleep EEG recorded over sensorimotor cortex is depicted in Figure 1.

RESULTS

Histology

The location and extent of the dorsal column lesions in each animal were determined by gross dissection and by the examination of serial sections of spinal cord. Representative photomicrographs showing the maximal extent of damage in animals of each experimental group are presented in Figure 2.

In five animals, tissue damage was restricted to the dorsal columns bilaterally; lesions in these animals ranged in extent from 70% to 95%. In four cases, the lesions extended into adjacent tissue including portions of the posterior horns and central grey. The remaining animals sustained virtually complete unilateral destruction of the dorsal columns contralateral to cortical EEG recording sites.

Sleep Spindle Activity

In agreement with our hypothesis, data showed that transecting the dorsal columns resulted in a significant increase in the incidence of 12-15 Hz sleep spindle activity over cortical sites corresponding to peripheral receptive fields below the level of the lesions. Results of bandpass analysis, depicted in Figure 3, disclosed significant enhancements of spindle activity over medial sensorimotor cortex after the placement of either high-cervical ($t=-2.78$, $p<0.05$) or low-cervical ($t=-3.78$, $p<0.05$) lesions. Animals with high-cervical lesions displayed a clear statistical trend toward increased spindle activity over lateral sensorimotor cortex as well ($t=-1.63$, $p<0.10$); there were, however, no significant pre/postlesion differences over these sites in animals of the low-cervical group.

Depicted in Figure 4 are representative pre/postlesion EEG tracings showing changes in cortical spindle activity over pericruciate cortical recording sites in an animal with dorsal column lesions at the high-cervical (C_1-C_2) level. As seen, spindles were enhanced over both medial and lateral sensorimotor cortex, at sites corresponding to somatosensory receptive fields of the hindlimbs and forelimbs (Rubel, 1971).

Seizure Susceptibility

All animals displayed a sequence of prodromal behaviors characteristic of acute MMH intoxication (e.g., piloerection, salivation, emesis, hyperventilation, hyperactivity). The most discrete of these behaviors, emesis, appeared within 45-minutes postinjection in all animals studied. Four animals of the high-cervical group

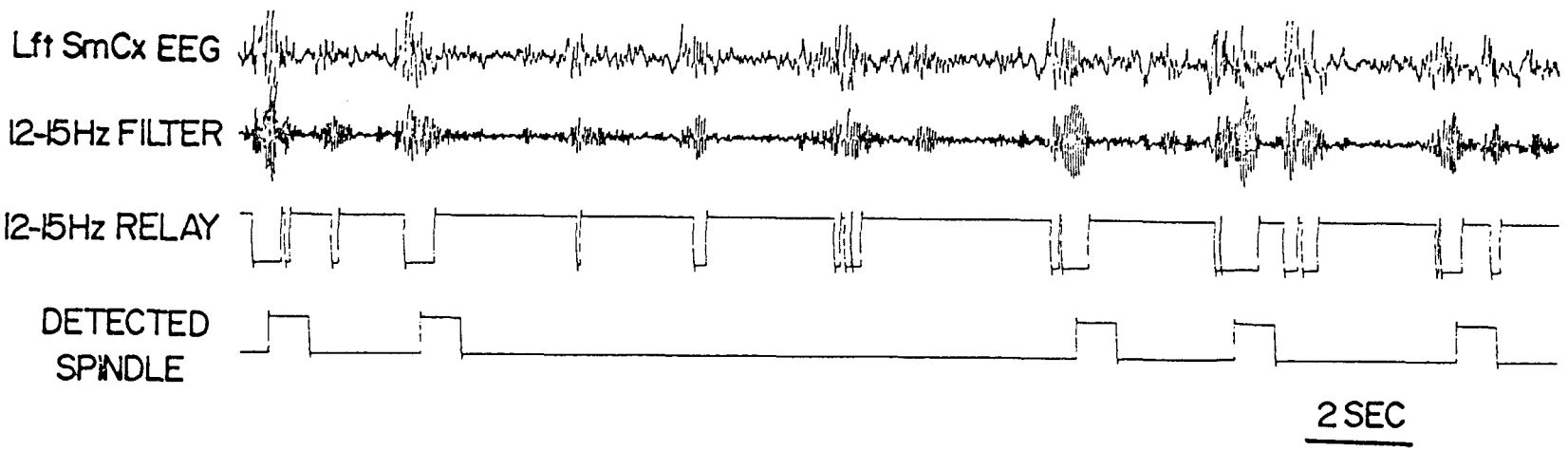


Figure 1. EEG tracing from left sensorimotor cortex showing the instrumental detection of 12-15 Hz spindle patterns in a segment of quiet-sleep.

exhibited seizure symptomology (e.g., forelimb myoclonus, facial twitching, motor akinesia) some time prior to the onset of generalized tonic-clonic convulsions. These episodes were short-lived and, in most cases, non-recurring.

Individual seizure latency values for animals of each experimental group are presented in rank order, together with group means and standard deviations, in Table 1. Included in this table are standard values previously reported for a large group of animals (N=18) prepared with indwelling cortical and subcortical electrodes only (Sterman, 1976; Sterman et al., 1977; Shouse and Sterman, 1979). Evaluation of these data disclosed no systematic relationship between seizure susceptibility and either weight or gender. As shown, seizure latencies for intact animals were extremely stable. Experimental group values displayed greater variability and, in general, were considerably larger than those of intact animals. High and low-cervical group latencies ranged from 70 to 222 minutes ($\bar{x}$=134 minutes) and 60 to 90 minutes (81.4 minutes), respectively. Examination of individual seizure latency values for animals of each group, depicted in Figure 5, clearly indicate a progressive reduction in seizure susceptibility with more encephalad dorsal column transections.

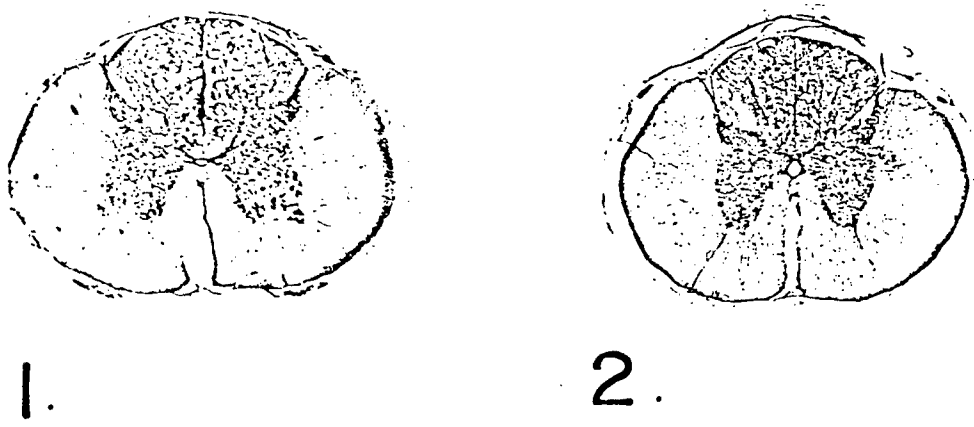
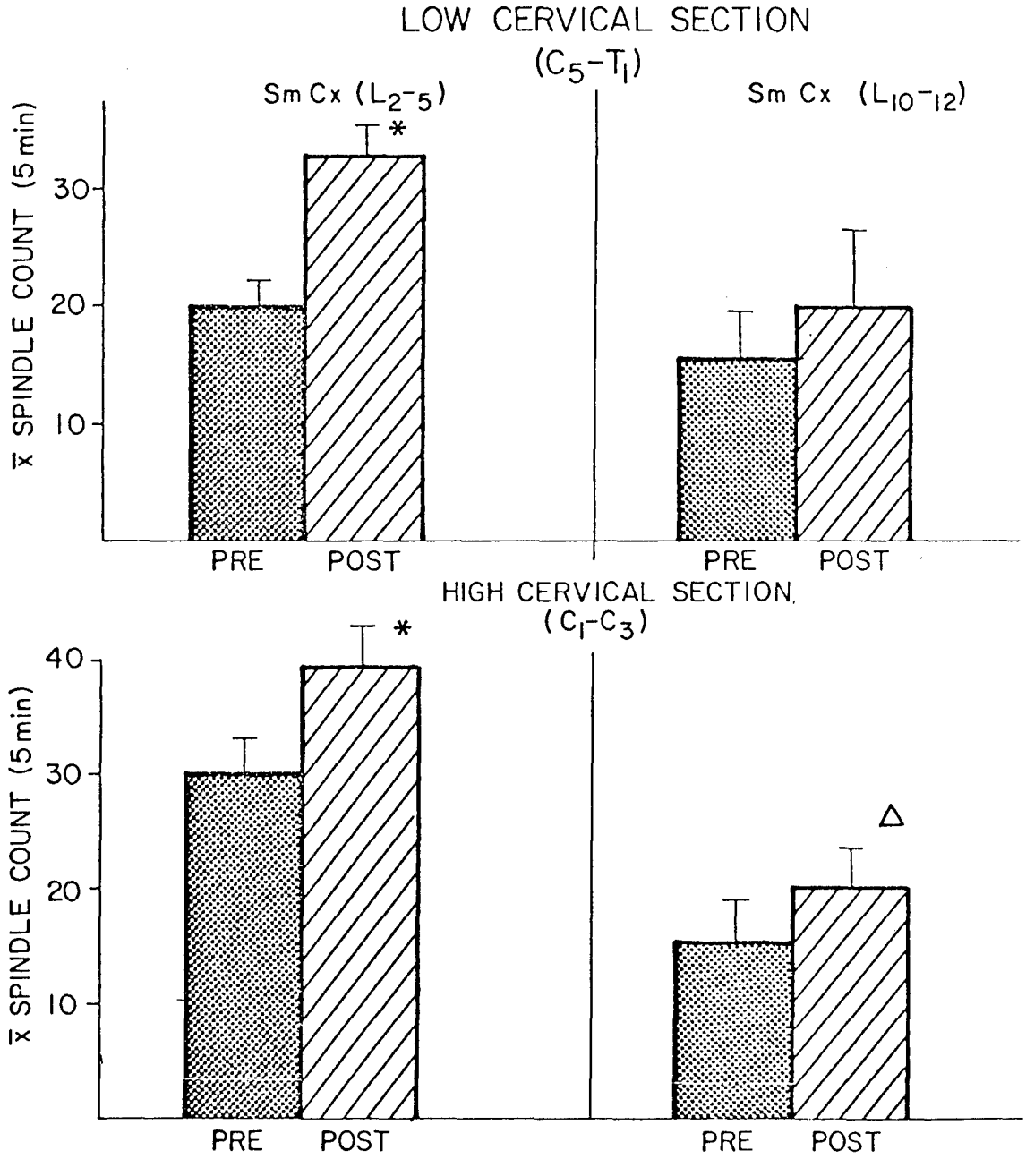


Figure 2. Coronal sections showing examples of histological material from animals with: 1. high-cervical (C_1- C_3) and 2. low-cervical (C_5-T_1) dorsal column lesions.

An Analysis of Variance revealed highly significant group differences (F=18.84, $p<0.001$). Multiple comparison t-tests of individual group data confirmed statistically significant differences between intact group latencies and those of both experimental groups (Intact vs. High-cervical: $t=-4.30$, $p<0.05$; Intact vs. Low-cervical: $t=-3.03$, $p<0.05$); however, there was no specific correlation between the extent of damage to the dorsal columns at each level and subsequent seizure latency (Spearman Rank Correlation Coefficient; High-cervical: $r_s=-0.77$, $p>0.25$; Low-cervical; $r_s=-0.58$, $p>0.25$). Seizure latency data for animals of each group are summarized in Figure 6.



* P<0.05

Δ P<0.10

Figure 3. Graph depicting the incidence of 12-15 Hz sleep spindle activity in animals of each experimental group before and after transection of the dorsal columns. As shown, placement of dorsal column lesions at either high (C_1-C_3) or low (C_5-T_1) cervical levels resulted in a significant enhancement of spindle activity over medial (L_2-$_5$) sensorimotor cortex.

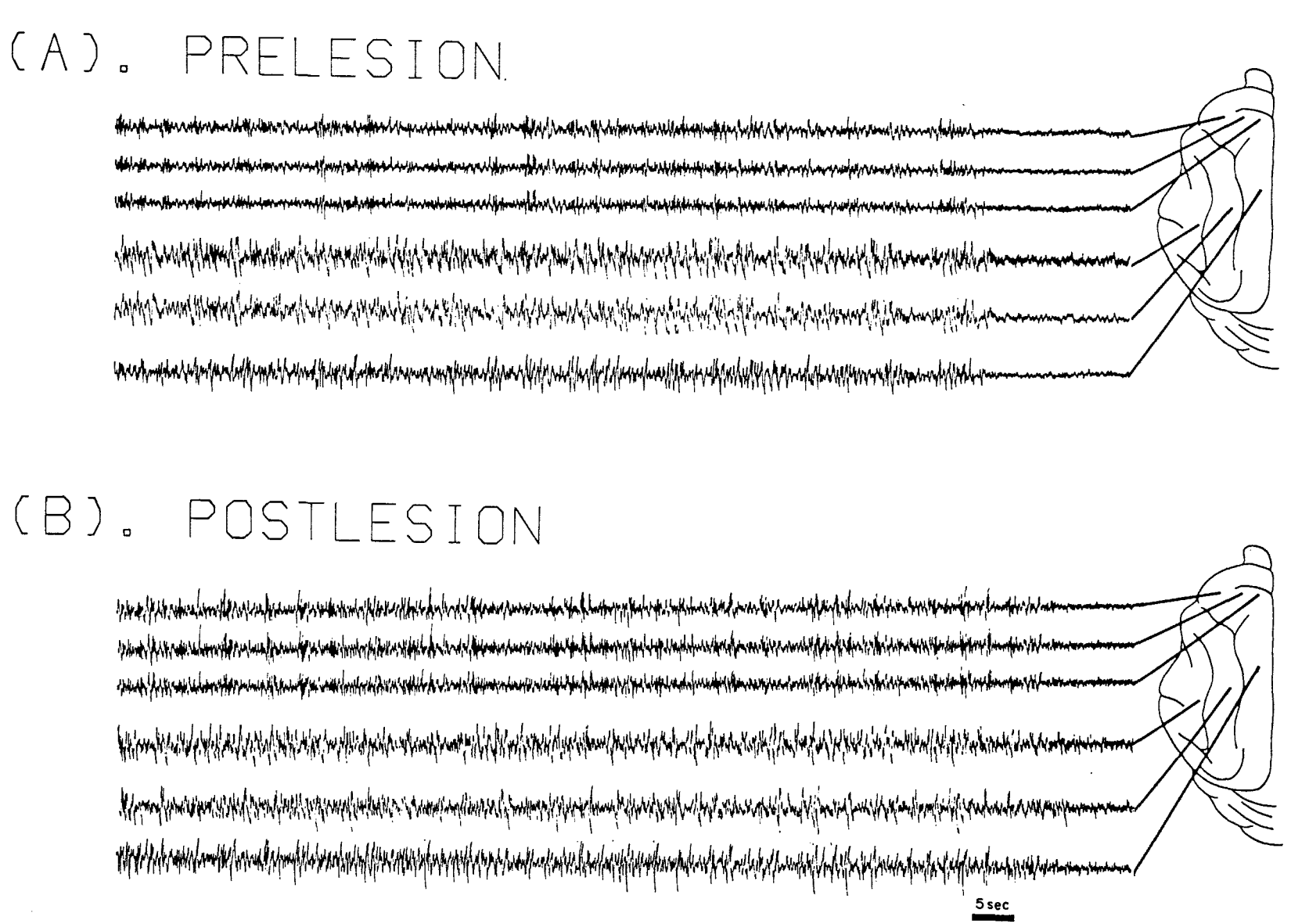


Figure 4. Polygraphic tracings showing cortical EEG activity in 2.5 minute segments of quiet-sleep preceding REM onset before (A) and after (B) transection of the dorsal column at the high-cervical level. Note increased spindle activity over sensorimotor cortex in the postlesion EEG segment.

Table 1. Seizure latency, weight, and gender data for cats of each experimental group. Data for the control group were obtained from previous investigation (Sterman, 1976; Shouse and Sterman, 1979); a complete roster of weight and gender information for this group was not available.

ANIMAL ID	LESION SITE	GENDER	WEIGHT (kg)	SEIZURE LATENCY (minutes)
145	C_5-C_6	M	3.15	60
104	C_6-C_7	M	3.59	74
101	C_6-C_7	F	3.09	90
164	C_7-T_1	M	2.67	90
1	C_7-T_1	F	2.67	93
$\bar{X}$				81.4
SD				14.09
139	C_1-C_2	F	4.74	70
113	C_1-C_2	M	4.41	86
142	C_2-C_3	M	3.07	131
132	C_1-C_2	M	4.32	142
124	C_1-C_2	F	4.46	153
170	C_1-C_2	F	3.35	222
$\bar{X}$				134
SD				53.99
1	-	-	-	41
2	-	-	-	45
3	-	-	-	48
4	-	M	5.22	52
5	-	M	4.18	54
6	-	F	3.07	54
7	-	-	-	56
8	-	F	6.02	57
9	-	-	-	57
10	-	M	4.04	62
11	-	-	-	62
12	-	-	-	63
13	-	M	5.34	64
14	-	M	5.63	67
15	-	-	-	67
16	-	F	3.86	70
17	-	-	-	76
18	-	-	-	80
$\bar{X}$				59.7
SD				10.24

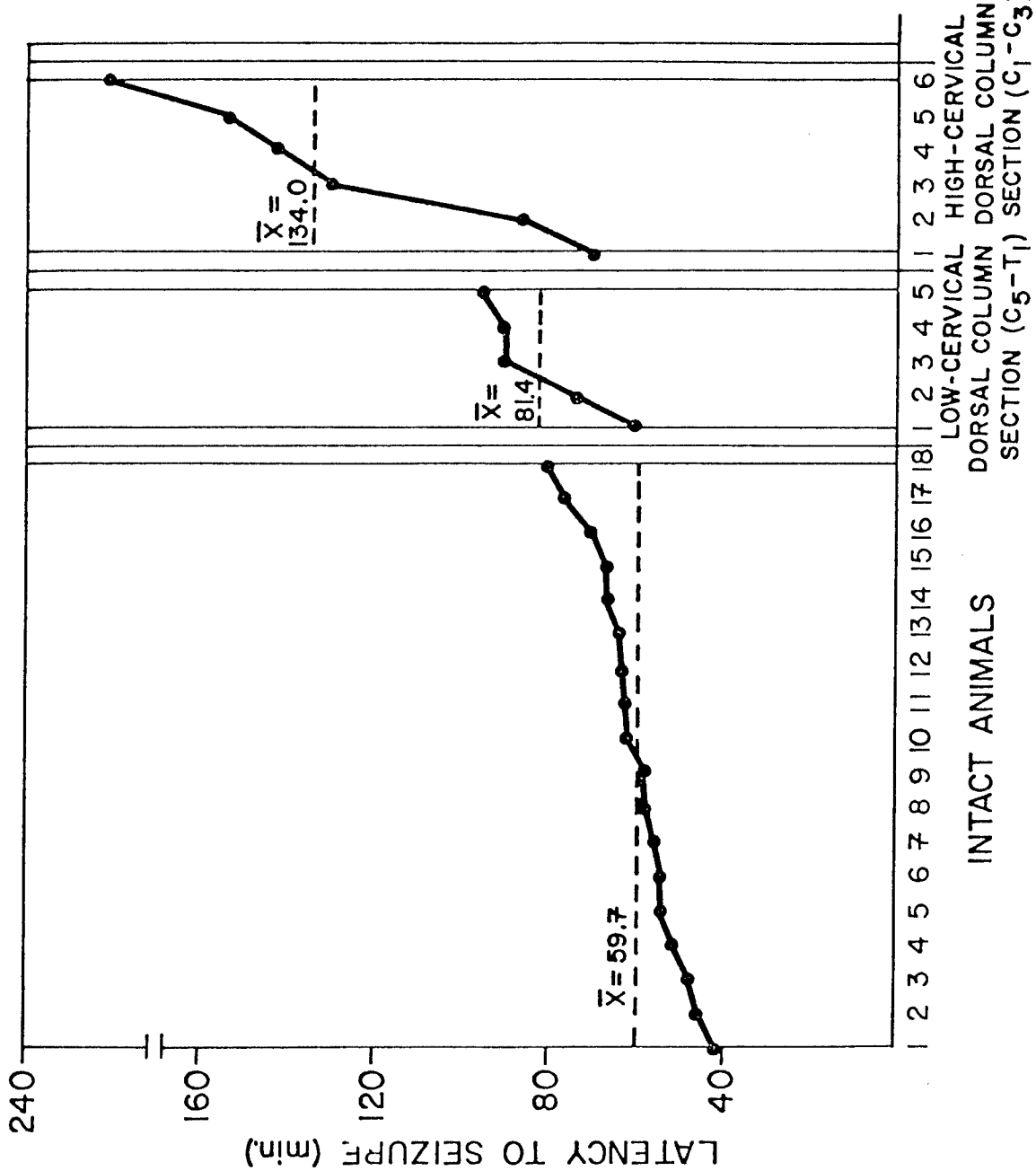


Figure 5. Graphic representation of MMH seizure latency values showing incremental increase in resistance to seizures with more encephalad dorsal column transections.

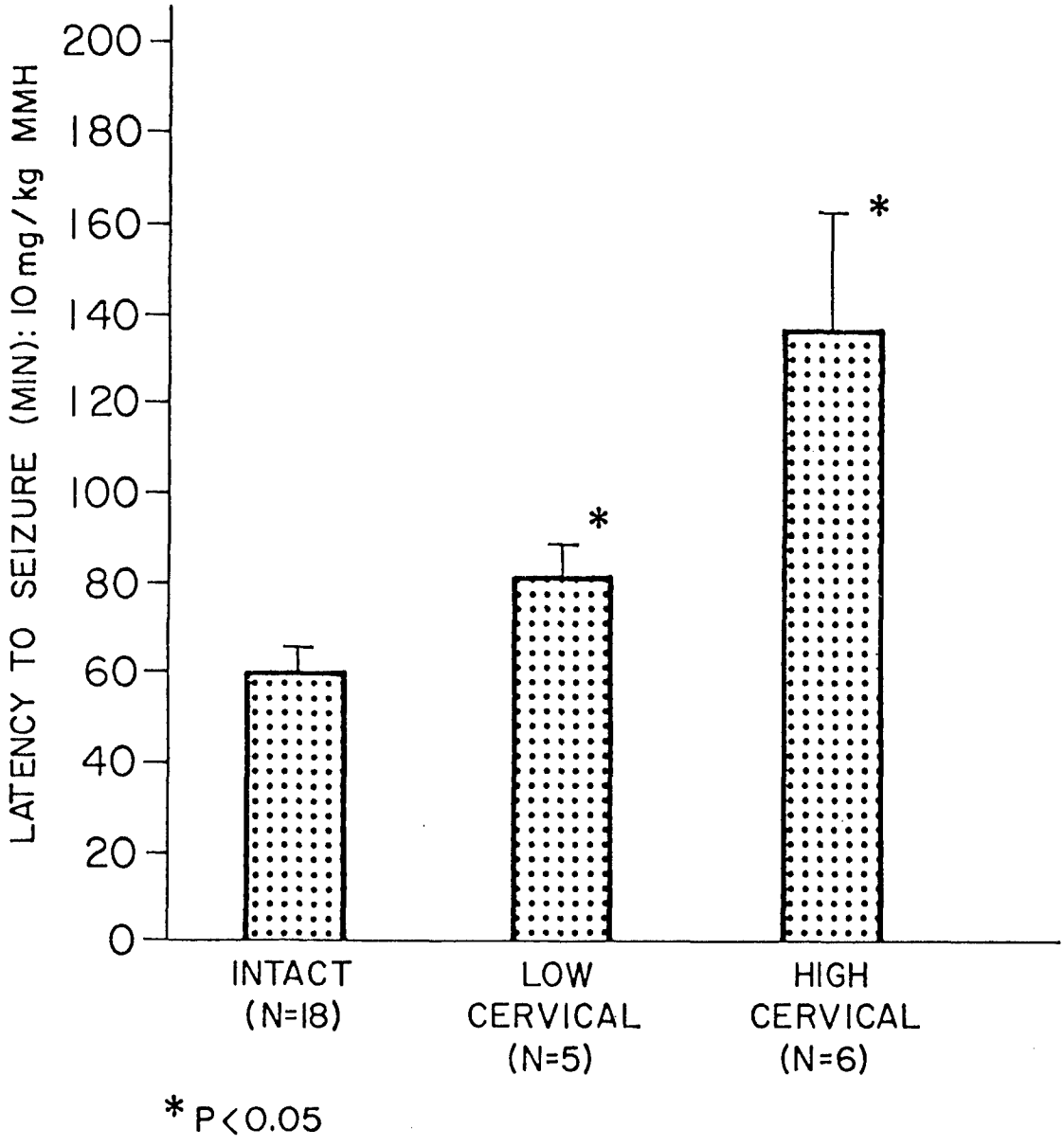


Figure 6. Graphic comparison of latency to MMH-induced convulsions in three groups of cats. The high- (C_1-C_3) and low- (C_5-T_1) cervical groups showed significantly greater latencies than the intact group.

DISCUSSION

Previous investigations in our laboratory indicated that the seizure response to intraperitoneal injections of 10 mg/kg monomethylhydrazine (MMH) was permanently altered in cats subjected to neurosurgical procedures; findings showed that the more extensive the surgical interventions the shorter the subsequent seizure latency (Sterman et al., 1976; 1977). In related studies, it was disclosed that the MMH-seizure response was extremely stable in animals surgically prepared with surface and indwelling cortical electrodes but otherwise intact (Sterman, 1976; Sterman et al., 1977; Shouse and Sterman, 1979). MMH response characteristics were unaffected by replication variables or by intrinsic differences between animals with respect to weight and gender (Sterman et al., 1977; Shouse and Sterman, 1979). These findings were important to the present investigation, first, because they assured that latency measures for electrode-implanted, intact animals established a reliable baseline reference for comparing the effects of somatosensory deafferentation and, second, because they indicated that the current findings were due to a specific neurophysiologic effect and not merely to deleterious side-effects of spinal surgery.

Data reported here are consistent with results of earlier investigations which reported a similar attenuation of MMH-induced seizures after functional somatosensory deafferentation produced by physical restraint (Bowersox et al., 1978; Sterman and Kovalesky, 1979) or the administration of neuromuscular blocking agents (Sterman et al., 1969). The current findings suggest an alternative hypothesis to conventional explanations which propose that protection against seizures is provided by the reduction of cutaneous and proprioceptive somatosensory inflow which normally constitute a source of convulsion inducing excitatory feedback. On the basis of the present findings, we suggest that the protective effect of somatosensory deafferentation upon MMH-induced seizures relates specifically to the enhancement of discrete 12-15 Hz EEG patterns over sensorimotor cortex. This hypothesis is consistent with results of previous studies indicating that 12-15 Hz sensorimotor cortical EEG patterns correlate with central suppressive or inhibitory processes (Hongo et al., 1963; Roth et al., 1967; Wyrwicka and Sterman, 1968; Chase and Harper, 1971). It agrees also with earlier findings showing that enhancement of these "sensorimotor rhythms" by specific behavioral manipulations result in a significant elevation of MMH seizure thresholds (Sterman et al., 1976; Sterman et al., 1978).

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